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Der(16)t(1;16)(q21;q13) in Wilms' Tumor: Friend or Foe

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The der(16)t(1;16)(q21;q13) chromosomal abnormality has been reported rarely in Wilms' tumor. This abnormality has also been found in several other pediatric and adult neoplasms, and may imply a poor prognosis in at least some of these solid tumors. To investigate its clinical significance in Wilms' tumor, we examined the records of 65 consecutive children with Wilms' tumor whose tumor cells were successfully karyotyped. The t(1;16) was present in seven patients (10%) whose ages ranged from 2.5 to 4.7 years (median 3.5 years) at diagnosis. Six of the seven patients were female. All four stages of Wilms' tumor were represented (two patients had stage IV disease). No patient had bilateral disease. All tumors were of "favorable histology." All seven patients are alive and off therapy with a median follow-up of 3.2 years (range, 2 to 8.5 years). One patient with this abnormality developed brain metastases within 4 months of completion of therapy. Comparison of these patients with the remaining 58 Wilms' tumor patients revealed no significant differences with regard to disease stage, histology, survival, or relapse-free survival. Cytogenetic evidence of der(16)t(1;16)(q21;q13) in Wilms' tumor does not appear to portend an adverse clinical outcome, although only a larger study that includes molecular detection methods can provide more conclusive evidence.

Key words: translocation, Wilms' tumor, prognosis

INTRODUCTION

The identification and characterization of tumor-specific chromosomal rearrangements has provided valuable clues to the diagnosis, prognosis, and ultimately the molecular events underlying malignant transformation [1–3]. Wilms' tumor (WT), which comprises almost all childhood renal neoplasms [4], is unique in its association with congenital disorders such as overgrowth disorders, aniridia, genital malformations, and others [5]. Additionally, specific chromosomal abnormalities have been associated with the development of Wilms' tumor. Patients with WT and associated syndromes (Wilms' tumor-aniridia-genitourinary malformation-retardation syndrome [WAGR] and Beckwith-Wiedemann syndrome [BWS]) have a constitutional deletion or rearrangement of the short arm of chromosome 11 [6]. Translocations in WT have also been reported [7], but the clinical importance of the der(16)t(1;16)(q21;q13) in this tumor has not been well elucidated. To characterize this abnormality and investigate its clinical significance, we compared the clinical features of patients whose tumor-cell karyotypes did (n = 7) and did not (n = 58) harbor this translocation.

MATERIALS AND METHODS

We reviewed the records of all patients with Wilms' tumor treated at St. Jude Children's Research Hospital from 1964 through 1992. Age at diagnosis, disease stage, treatment, and outcome data were recorded for the 65 patients who had successful tumor cytogenetic analysis. Disease stage was established according to the criteria of the National Wilms' Tumor Study [8]. Chromosome analysis was performed on direct preparations, short term cultures, or extended cultures of tumor cells using standard techniques, as described previously [9].

The demographic features and presenting features of patients with and without the translocation were compared using Fisher's exact test. This test is used for small sample sizes and unbalanced data. The Kaplan-Meier plots were compared using the exact log-rank test for small sample sizes and unbalanced data.

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Table I. Presenting Features of the 65 Karyotyped Wilms' Tumor Patients

Features	Translocation t(1;16)	No translocation n (%)	*P* value*
Sex			.41
Male	1 (14)	22 (38)	
Female	6 (86)	36 (52)	
Race			1.0
White	5 (71)	43 (74)	
Black	2 (29)	15 (26)	
Diagnosis age[a]			.83
<1	0 (0)	5 (9)	
1–3	5 (71)	29 (50)	
4+	2 (29)	24 (41)	
Site			.88
Kidney-right	4 (57)	26 (45)	
Kidney-left	3 (43)	23 (40)	
Kidney-bilateral	0 (0)	8 (14)	
Retroperitoneal	0 (0)	1 (1)	
Stage			.85
I	1 (14)	12 (21)	
II	2 (29)	12 (21)	
III	2 (29)	18 (31)	
IV	2 (29)	9 (15)	
V	0 (0)	7 (12)	
Histology			.47
Favorable	7 (100)	43 (74)	
Unfavorable	0 (0)	13 (23)	
Not evaluable	0 (0)	2 (3)	

*Two-sided Fisher's exact *P* value.
[a]Age at diagnosis range: 3.4 months to 11.5 years.

RESULTS

Seven patients with der(16)t(1;16)(q21;q13) were identified. Their clinical and pathological features are summarized in Table I. There were six females and one male. Age at diagnosis ranged from 2.5 to 4.7 years (median 3.5 years). None had bilateral Wilms' tumor. Family history was negative for major genitourinary abnormalities or Wilms' tumor. One patient had state I WT, two had stage II, two had stage III, and two had stage IV disease. Both patients with stage IV had pulmonary metastases. Pathological analysis showed favorable histology in all seven cases. All patients were treated on uniform protocols defined by stage and histology [10]. All patients had surgical tumor excision plus chemotherapy (depending on stage) consisting of vincristine, adriamycin, and dactinomycin. One patient with stage IV disease also received ifosfamide, carboplatin, and etoposide after having only a partial response to standard chemotherapy. All stage III and stage IV patients received radiation therapy to the primary tumor site. One stage IV patient also received cranial irradiation for brain metastases after she presented with seizures within 4 months after completion of therapy.

Table I compares the clinical characteristics of the seven patients who had the tumor cell t(1;16) with those of the 58 patients who did not have the translocation. No statistically significant difference was noted between the two groups with regard to age at diagnosis, site of Wilms' tumor, disease stage, or histology. The seven patients were followed for a median period of 3.2 years (range, 2.0–8.5 years). All but one patient have survived without complications and have been off therapy for 2 to 7.5 years. Follow-up was similar for the remaining 58 patients. The overall survival and relapse-free survival estimates are shown by the Kaplan-Meier plots in Figures 1 and 2, respectively. In overall survival, no statistically significant difference was seen between patients with the translocation and those without ($P = 0.39$). None of the patients with the translocation had expired as of this follow-up. Eleven (19%) patients without the translocation died of progressive disease within 3 years of diagnosis, and one expired after 5 years from an unrelated cause. We found no statistically significant difference in relapse-free survival between patients with and without the translocation ($P = 0.99$). However, our power to detect a significant difference was limited by the small sample size. Interestingly, the time to relapse was shortest (<4 months) in a patient with the translocation. The site of recurrence (brain) was also unusual in this patient.

In all seven patients with the t(1;16)(q21;q13), the translocation between the long arms of chromosomes 1

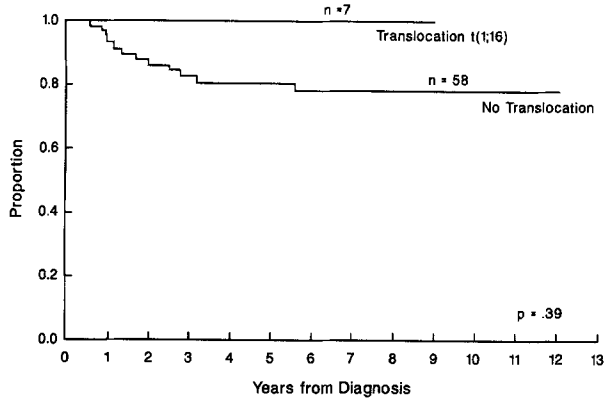

Fig. 1. Kaplan-Meier plot demonstrating survival estimates in 65 patients with karyotyped Wilms' tumor.

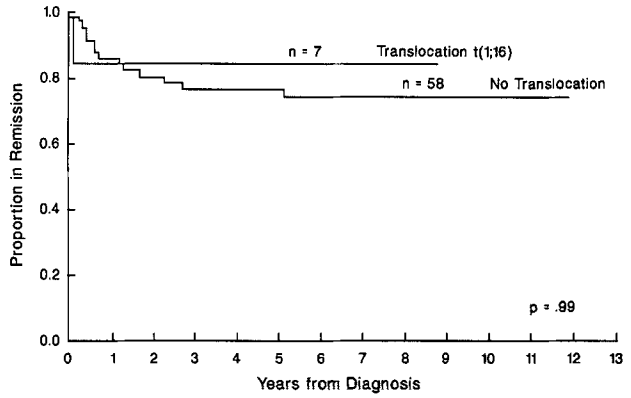

Fig. 2. Kaplan-Meier plot demonstrating relapse-free survival estimates in 65 patients with karyotyped Wilms' tumors.

and 16 resulted in partial trisomy of chromosome 1q and partial monosomy of chromosome 16q (Fig. 3). This translocation is usually non-reciprocal, with der(1) being almost always lost and der(16) being preferentially retained {der(16)t(1;16)(q21;q13)}. Flow cytometric analysis revealed four cases to be diploid and two to be hyperdiploid (DNA indices of 1.13 and 1.31). DNA index for one of the patients was not available. The t(1;16) was the only recurrent translocation found in the tumors studied.

DISCUSSION

Our report represents the first large patient series describing the der(16)t(1;16)(q21;q13) in Wilms' tumor. Patients whose tumor cells had the translocation were similar to others without the translocation, and were representative of patients reported in the literature in regard to age at presentation and in disease stage [11]. Despite our limited power to detect a statistically significant difference, all patients with the t(1;16) had favorable histology, all patients survived, and all but one had a relapse-

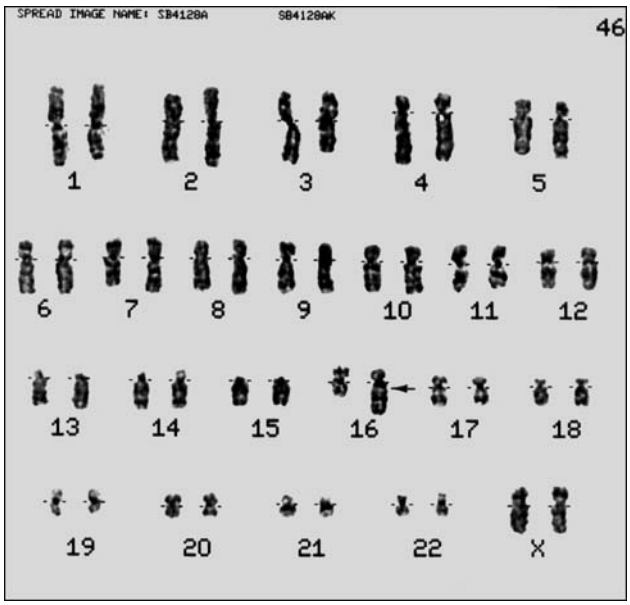

Fig. 3. Photomicrograph showing the karyotype of a Wilms' tumor cell with the der(16)t(1;16)(q21;q13).

free survival, irrespective of disease stage. We had anticipated that this translocation might imply a poor prognosis. However, this did not prove to be the case in our series.

The first cytogenetic study of Wilms' tumor was reported by Kaneko et al. [12] in 1981. Since then, karyotypic findings have been documented for 152 tumors [6]. Current cytogenetic data implicate three chromosomal loci in the development of Wilms' tumor—11p13, 11p15 and one on 16q [6,13]. Other loci are indirectly implicated by the exclusion of linkage between familial Wilms' tumor and the loci on 11p, the association of Wilms' tumor with neurofibromatosis type I (linked to chromosome 17q11.2), and the presence of putative precursor lesions of Wilms' tumor in the kidneys of patients with trisomy 13 and 18, as summarized by Maw et al. [13]. Translocation breakpoints in the long arm of chromosome 1 are particularly clustered in band 1q21. Most of these translocations are unbalanced and result in trisomy for this region, as we found in our seven cases. The cytogenetic abnormalities in chromosome 16 involve bands 16q11 and 16q13 [6].

In the series by Wang-Wuu et al. [7], abnormalities of 16p/16q were seen in 5 of 31 Wilms' tumors evaluated. However, only three of the tumors had a der(16)-t(1;16)(q21;q13). Of the three patients in their series who expired within 1 year of diagnosis, one had the der(16)t(1;16)(q21;q13). This patient had stage IV disease with favorable histology. Kaneko et al. [14] reported on two patients with Wilms' tumor who had the t(1;16), both of whom did well with therapy (surgery plus chemo-

therapy with vincristine and dactinomycin). Both had blastemal-predominant histology, but different breakpoints in each chromosome—t(1;16)(q21?;q22?) and t(1;16)(q11?;q11?). Kondo et al. [15] found chromosome 1 abnormalities in five of nine Wilms' tumor patients, all of which resulted in a partial trisomy of the long arm (q21-q31). Chromosome 16 abnormalities were noted in three cases resulting in partial monosomy of the long arm and a common deletion of 16q22. Two had a translocation involving 1q and 16q. All had favorable histology and survived.

Kondo et al. [15] postulated that trisomy 1q may be related to malignant progression (proliferative advantage of the tumor cells) rather than malignant transformation (origin of the tumor). In a patient reported by Wang-Wuu et al. [7], the t(1;16)(q21;q13) was present in the main tumor mass but absent in a tumor nodule, supporting this suspicion. Recently, Maw et al. [13] reported data on loss of heterozygozity (LOH) that indicated a potential tumor suppressor gene for Wilms' tumor in the 16q13-qter region. Grundy et al. [16] reported on the significant association of 16q LOH and an adverse outcome in Wilms' tumor, suggesting that the underlying genetic locus may be involved with tumor progression rather than initiation, and that the genetic event may occur in an already established tumor, resulting in further growth advantage to the tumor cells or an increased ability to metastasize. The fact that one of our patients with this translocation had metastases to an unusual site (brain) for Wilms' tumors, and within a short time after therapy, may be relevant in this regard. Although the partial monosomy caused by the unbalanced translocation could have resulted in loss of genetic material from 16q, the few patients in our series did not show any relevant clinically significant impact. Newsham et al. [17] recently reported a constitutional BWS-related translocation occurring in the same region of chromosome 16 (region encompassing distal 16q13 and proximal 16q22) implicated in Wilms' tumors. However, this translocation, unlike those in our patients, was balanced and this may have had different genetic consequences.

The t(1;16) has also been reported as a secondary structural abnormality in Ewing's sarcoma [18,19], peripheral neuroectodermal tumors [19] and rhabdomyosarcoma [20]. Of the four patients reported by Douglass et al. [19] with Ewing's sarcoma and with the t(1;16), three did not survive. While the genes involved in the t(1;16) have yet to be identified, it is conceivable that this translocation results in the creation of a novel hybrid gene product that could affect the growth and differentiation of the tumor. In this regard, studies in nude mice [21] have suggested that trisomy 1q plays a role in the tumorigenicity and metastatic potential of human leukemic B-cell clones. Although our clinical data did not reveal any adverse outcome associated with this translocation, outcomes are favorable overall for patients with Wilms' tumor, and a larger study is needed to confirm our findings. As well, the availability of molecular genetic assay techniques may reveal the abnormality in a larger subset of patients than hitherto identified.

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